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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/802,094	03/08/2001	Paul Calabresi	21486-038	4935

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EXAMINER	
YAEN, CHRISTOPHER H	

ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 03/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/802,094	CALABRESI ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9 and 11-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9 and 11-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed 12/20/2002 (paper no 16) is acknowledged and entered into the record. Accordingly, claims 1-8, and 10 are canceled, claims 9, 12,13,18,19, and 20 are amended.

2. Therefore, claims 9, 11-20 are pending and examined on the record.

Information Disclosure Statement

3. The information disclosure statement filed, 7/18/2001 (paper no 9) was not initialed in the last office action because a copy of the IDS was missing. An additional copy was filed 12/20/2002. A signed copy is attached hereto.

Claims Rejections Withdrawn - 35 USC § 102

4. The rejection of claims 9,11,14,15,16, and 20 under 35 USC 102(b) as being anticipated by O'Leary *et al* is withdrawn in view of the amendments and persuasive arguments set forth by the applicant.

Claim Rejections Withdrawn - 35 USC § 103

5. The rejection of claims 9 and 11-20 under 35 USC 103 (a) as being obvous over O'Leary *et al* in view of Sheibani *et al* and Streit *et al* is withdrawn in view of the amendments and persuasive arguments set forth by the applicant.

NEW GROUNDS OF REJECTION

Claims Rejections - 35 USC § 112, 2nd paragraph

6. Claims 9, 11-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. With regard to the terms "thrombospondin compound" and "inhibitor of DNA topoisomerase I", it is unclear as to which compounds and inhibitors that are being referred. There are many compounds or inhibitors that fall within the scope of these terms. As such the metes and bounds of the term cannot be adequately determined.

8. Claims 9, 11-20 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps include the recitation of how the inhibition of tumors are to take place. Do applicant intend for the tumors or cancer to be eliminated or inhibitd by the simple addition of compounds?

Claims Rejections - 35 USC § 112, 1st paragraph

9. Claims 9, 11-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting colon cancer tumor growth comprising the administration of water soluble camptothecin compounds in conjunction with TSP-1 and/or TSP-2, does not reasonably provide enablement for a method of inhibiting any and all cancer cells or tumors comprising the administration of any and all DNA topoisomerase I inhibitors and any and all thrombospondin compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims of the invention are drawn to a method of inhibiting tumor cell growth comprising the administration of a DNA topoisomerase I inhibitor and a thrombospondin compound. The specification teaches that the administration of a camptothecin

molecule, a DNA topoisomerase inhibitor, with TSP-1 or TSP-2 is able to inhibit the growth of tumor cells. The applicant's contend that the instant invention differs from the prior art in that the combination of camptothecin and TSP-1 or TSP-2 has a synergistic effect causing an increased amount of tumor cell growth retardation/elimination. The specification also teaches that not all camptothecin molecules are predictable or safe and that the use of two specific kinds of water soluble camptotecin molecules are safer and better tolerated (see page 3 lines, 23-29). The specification also teaches that TSP-1 or TSP-2 have type-I properdin repeats that exhibit anti-angiogenic effects. And lastly, the specification discloses in the form of a working example, the inhibition of colon caner cells in a nude mice model wherein the mice were administered either TSP alone, CPT-11, or TSP plus CPT-11. However, the specification has not taught how to use any other form of DNA topoisomerase inhibitor excepts for water soluble forms of camptothecins, nor has the specification taught what other thrombospondin other than TSP-1 and TSP-2 can be used in the instant invention. Furthermore, the working examples of the instant invention have only taught the inhibition of colon cancer cells and not any other cancer cell. One of skill in the art would be forced into undue experimentation to practice the instant invention because the skilled artisan would not know which other inhibitors or thrombospondins could be used in the instant invention. The artisan would essentially have to determine on their own how and which inhibitors and thrombospondins are suitable to fulfill the essential requirements of the invention. As it was stated in the specification, not all camptothecins are safe or predictable for treatment due to its cytotoxic effects, therefore, one of ordinary skill in the art would be

forced to determine which camptothecin inhibitors are suitable for usage (see page 3). Furthermore, the specification has not taught any other forms of DNA topoisomerase inhibitors other than the camptothecin family. Surely, not all topoisomerase inhibitors are effective in inhibiting cancer cells. Further still, the specification teaches that there are potentially five different forms of thrombospondin, wherein TSP-5 lacks heparin binding domains, because there are inherit differences between the different TSP, and because the art and the specification has only accepted TSP-1 and TSP-2 as having anti-angiogenic activities, the skilled artisan would be forced to determine if the application of other TSPs to the instant method would produce the same results. Currently, the specification has only provided information on two forms of TSP. Because there is a lack of disclosure teaching the effects of the other forms of TSP, the skilled artisan would be forced to conduct large quantities of undue experimentation. And lastly, it is a well known fact and excepted understanding in the art that cancer and cancer treatment is an unpredictable disease, wherein the etiology and origin of cancer cells determine the outcome and course of treatment. Because the specification has only taught the inhibition of one type of cancer, namely, colon cancer, the skilled artisan would need to determine whether the instant invention would apply to all cancer types, such as leukemias or lymphomas. Because the specification is devoid of such teachings, the artisan would be forced to experiment.

Therefore, considering large quantity of experimentation needed, the unpredictability of the field, the state of the art, and breadth of the claims, it is concluded that undue experimentation would be required to enable the intended claim. Many of

these factors have been summarized *In re Wands, 858 F.2d 731, USPQ2d 1400 (Fed. Cir. 1988)*.

New Claim Rejections - 35 USC § 103

10. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

11. Claims 9, 11-15, and 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Joshi *et al* (WO 99/54445A2; **IDS BA**) in view of O'Leary *et al* (**IDS CI**), Sheibani *et al* (Biochem Biophys Res Commun 2000 Jan;267(1):257-61, cited in the prior office action), and Streit *et al* (PNAS USA 1999, Dec;96(26):14888-93, cited in the prior office action). Claims are drawn to a method comprising the administration of a DNA topoisomerase inhibitor and a thrombospondin (TSP) compound, wherein the inhibitor is a camptothecin (further limited to CPT-11 or topotecan) and the TSP is TSP-1 or TSP-2. The claims are further limited to the administration intervals of the inhibitor and TSP. Joshi *et al* disclose a method comprising the steps of administering a therapeutic gene that encodes an anti-angiogenic compound and DNA topoisomerase inhibitor. Joshi *et al* do not specifically teach the type of anti-angiogenic compound nor do they teach the type of topoisomerase inhibitor.

However, O'Leary *et al*, Sheibani *et al* and Streit *et al* do teach the topoisomerase inhibitor, and the types of TSPs used. O'Leary specifically teaches that camptothecin compounds such as CPT-11 and topotecan exhbit anti-angiogenic properties and disclose the use of these compounds in the administration in a mouse model. Sheibani *et al* and Streit *et al* also teach the use of TSP-1 and TSP-2,

respectively, and the anti-angiogenic properties these molecules have on animal models.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to inhibit tumor cell growth with a method of administering anti-angiogenic compounds and DNA topoisomerase inhibitors, because the basic method was already taught. The skill artisan would have known to combine the generic method of Joshi *et al* with that of O'Leary *et al* , Sheibani *et al* and Streit *et al* to substitute the specific required compounds to derive at the instant method. One of ordinary skill would have been motivated to combine the reference because the generic method Joshi *et al* suggest the use of anti-angiogenic compounds with that of DNA topoisomerase inhibitors. The teachings of O'Leary *et al*, Sheibani *et al* and Streit *et al* provide the skilled artisan with the specific inhibitors or TSPs that Joshi *et al* suggest in their specification and disclosure. One of skill in the art would have expected a reasonable amount of success in substituting the specific inhibitors or TSPs into the generic method of Joshi *et al* because each specific inhibitor or TSP was shown to be effective as an anti-angiogenic inhibitor independently. The administration of the compounds together would inherently exhibit the same effect of inhibiting tumor cell growth when applied to a subject.

Conclusion

No claim is allowed. This action is made NON-FINAL in view of the new arguments made in this office action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
March 24, 2003

ALI R. SALIMI
PRIMARY EXAMINER